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Associations of functional connectivity and walking performance in multiple sclerosis

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ABSTRACT

Background: Persons with multiple sclerosis (MS) often demonstrate impaired walking performance, and neuroimaging methods such as resting state functional connectivity (RSFC) may support a link between central nervous system damage and disruptions in walking.
Objectives: This study examined associations between RSFC in cortical networks and walking performance in persons with MS.
Methods: 29 persons with MS underwent 3-T brain magnetic resonance imaging (MRI) and we computed RSFC among 68 Gy matter regions of interest in the brain. Participants completed the Timed 25-foot Walk as a measure of walking performance. We examined associations using partial Pearson product-moment correlation analyses (r), controlling for age.
Results: There were eight cortical brain regions that were significantly associated with the T25FW, including the left parahippocampal gyrus and transverse temporal gyrus, and the right fusiform gyrus, inferior temporal gyrus, lingual gyrus, pericalcarine cortex, superior temporal gyrus, and transverse temporal gyrus.
Conclusions: We provide novel evidence that RSFC can be a valuable tool to monitor the motor and non-motor networks impacted in MS that relate to declines in motor impairment. RSFC may identify critical nodes involved in a range of motor tasks such as walking that can be more sensitive to disruption by MS.

1. Introduction

Multiple sclerosis (MS) is a chronic neurological disease characterized by inflammation, demyelination and transection of axons, and neurodegeneration within the central nervous system (CNS) (Trapp and Nave, 2008). Persons with MS often demonstrate impaired walking performance, ostensibly a result of the damage in the CNS (Motl, 2013). Neuroimaging methods can provide a link between focal damage to the CNS and disruptions to walking, and this is an emerging area of literature that has largely focused on regions of interest (Motl et al., 2015) and tracts (Hubbard et al., 2016).

Functional magnetic resonance imaging (fMRI) during the resting state (RS) may be an effective technique for examining the neural correlates of walking performance in MS (Sbardella et al., 2015). This technique temporally correlates spontaneous, low-frequency fluctuations in the blood-oxygen-level-dependent (BOLD) signal that are temporally coherent across anatomically separate brain regions at rest as a measure of functional connectivity (FC) (Ogawa and Lee, 1990; Filippi and Rocca, 2013). Resting state functional connectivity (RSFC) relies on the same BOLD signal mechanism that would present during a task-based fMRI scan, and hence this signal represents neural activity, including neurotransmitter turnover and metabolism (Attwell and Iadecola, 2002). Importantly, RSFC may elucidate the networks involved with walking performance as well as the impact of CNS damage, providing a potential to monitor disease progression or intervention efficacy.

A recent study examined the associations of RSFC at the cortical and subcortical levels with disability and cognitive impairment in persons with MS (Rocca et al., 2017). That study analyzed four cortical hubs, including specific brain regions representing the default mode network (DMN), dorsal attention network (DAN), sensorimotor network, and the visual network; and three subcortical hubs, including specific brain

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regions representing the cerebellum network, thalamic network, and reward-emotion network. The results indicated that higher disability (i.e., Expanded Disability Status Scale (EDSS) scores) was significantly correlated ($p < 0.05$) with reduced RSFC in the DMN, DAN, and the sensorimotor network (Rocca et al., 2017). Worse performance in the attention, verbal, and visual memory domains of neuropsychological measures (i.e., the Brief Repeatable Battery of Neuropsychological Tests) were significantly correlated with reduced global RSFC in the DMN and DAN and reduced regional RSFC in the cognitive, sensorimotor, cerebellar, and subcortical networks (Rocca et al., 2017). However, other research on RSFC in persons with MS have been somewhat contradictory as some studies demonstrated cognitive impairment to be associated with reduced RSFC (Rocca et al., 2010; Bonavita et al., 2011) in cognitive-related networks, while other studies demonstrate increased RSFC (Hawallek et al., 2011; Faivre et al., 2012).

Previous research in healthy populations has demonstrated that locomotion, or walking, is associated with brain activation in several brain regions, including parietal, parahippocampal, and prefrontal regions that are associated with spatial navigation, memory, and executive function (Hamacher et al., 2015). For example, a study in a sample of healthy older adults examined RSFC and gait velocity in normal walking and dual task (DT; i.e., walking while talking) conditions (Yuan et al., 2015). That study demonstrated gait velocity in both conditions to be significantly and positively associated ($p < 0.05$) with RSFC, such that faster gait velocity was associated with higher RSFC. This was specifically apparent in the sensorimotor (premotor, primary motor, and supplementary motor cortices), visual (primary, secondary, and associative visual cortices), vestibular (insula and the primary and secondary auditory cortices), and left frontal parietal (left posterior parietal association areas, left supplementary motor cortex, left frontal eye field, and left prefrontal association cortex) areas (Yuan et al., 2015). The networks associated with gait velocity in the DT condition demonstrated significantly greater FC in supplementary motor and prefrontal regions, when compared to the normal walking condition (Yuan et al., 2015). In persons with MS, two previous studies demonstrated that corticospinal motor pathway damage, measured using diffusion tensor imaging, was associated with walking performance (Hubbard et al., 2016; Fritz et al., 2017) in persons with MS. However, these studies did not examine the neural correlates of walking performance in persons with MS at the cortical level.

To that end, this novel and exploratory study examined the associations of RSFC in cortical motor and non-motor (i.e., sensory, spatial, and attention) networks with walking performance (i.e., the Timed 25-foot Walk (T25FW)) in participants with MS. By focusing on cortical RSFC, we believe this study will help to identify critical FC nodes involved in MS-related degradations in walking performance. Importantly, cortical nodes identified as critical to walking performance in MS may potentially provide targets to monitor for early responses to behavioral interventions, such as physical activity, for the promotion of improved walking performance.

2. Materials and methods

2.1. Participants

A University Institutional Review Board approved the methods, and participants provided written informed consent. Participants were recruited through targeted advertisements disseminated in central Illinois. The inclusion criteria were confirmed diagnosis of MS, relapse-free within the past 30 days, not taking monthly medications for ongoing relapse, ambulatory with or without an assistive device, between the ages of 18 and 64, being right-handed, and willingness to undergo an MRI. Participants who screened positive for MRI contraindications were excluded from the study. 29 participants satisfied inclusion criteria and were enrolled in the study. Participants first underwent a neurological examination administered by Neurostatus-certified research personnel for Expanded Disability Status Scale (EDSS) scoring (Kurtzke, 1983), and all participants completed the T25FW and underwent an MRI within 14 days of the initial testing.

2.2. Timed 25-foot walk (T25FW)

The T25FW was administered as a measure of walking speed (Motl et al., 2017). Participants were instructed to walk as quickly and as safely as possible over a 25-ft course on a carpeted surface. One researcher recorded the participant's time (s) over two trials. Scores were averaged and then converted into walking speed (ft/s) in order to normalize the distribution (Hobart et al., 2013).

2.3. MRI acquisition and analysis

High resolution 3D T_1-weighted structural brain images were acquired using a whole-body Siemens Trio 3-T MRI scanner (Erlangen, Germany) using a magnetization prepared, rapid acquisition gradient echo (MPRAGE) sequence and the following parameters: 23 cm field of view, 256 × 256 × 192 matrix size with a 0.9 mm isotropic resolution, echo time (TE)/repetition time (TR)/inversion time (TI) of 2.32/1900/900 ms, flip angle of 9°, and generalized autocalibrating partially parallel acquisitions (GRAPPA) accelerated factor of 2 (Griswold et al., 2002). In addition, RS fMRI data was acquired using a gradient echo, echo planar imaging (EPI) acquisition with the following parameters: 38 slices, 3 mm slice thickness and 10% slice gap, TE/TR of 25 ms/2 s, 92 × 92 matrix size with a 23 cm field of view, parallel imaging using a GRAPPA accelerated factor of 2, and a resulting spatial resolution of 2.5 × 2.5 × 3.3 mm. 300 volumes were collected in the RS acquisition, which lasted for 10 min. Participants were instructed to keep their eyes open during the scan.

2.4. Preprocessing pipeline

DICOM format files acquired from the MRI scanner were first converted into the NIfTI format and then taken through a multi-step pipeline (Chou et al., 2012) relying heavily on FMRIB Software Library (FSL) (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009) and the Nipype python module (Gorgolewski et al., 2011). After converting the data to radiological (LAS) orientation, the first four time points of the time series were discarded. Then, the data were algorithmically corrected for slice acquisition timing and then FSL's MCFLIRT tool for motion registration was applied to the functional data (Jenkinson et al., 2002a, b). After registration, the six motion parameters were regressed from the time series. The timewise mean of the functional data was then calculated and used as a reference for FSL's brain extraction tool (BET) to skull strip the dataset (Jenkinson et al., 2002a, b). The functional dataset was then resampled into a 2 mm isotropic analysis space, to minimize interpolation and increase the computational efficiency of the preprocessing pipeline as an alternative to carrying out processing in the structural space. A transformation to this analysis space was then computed for the T_1-weighted sagittal MPRAGE structural image using FSL's Linear Image Registration Tool (FLIRT) (Jenkinson et al., 2002a, b; Jenkinson and Smith, 2001), to be applied to a semi-automated cortical Freesurfer parcellation (Desikan et al., 2006; Fischl et al., 2004) generated from the structural data, as well as white matter (WM) and cerebrospinal fluid (CSF) masks generated using FSL's Automated Segmentation Tool (FAST) (Zhang et al., 2001). The Freesurfer-based parcellation used in this study included manual edits by a trained analyst to correct common tissue misclassifications, according to the methods recommended on the Freesurfer website (Freesurfer Tutorial, 2017). The WM and CSF signals were then regressed from the dataset, and the data were bandpass filtered to remove low frequency motion signals and high frequency noise.